

INTERNATIONAL SEARCH REPORT

C261

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| International application No |
| PCT/US2007/016023 |

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/295 A61K31/52 A61K31/409 A61K33/26 A61K45/00
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|------------------------|
| X | WO 03/088745 A (VON KROSIKG JAMES RICHARD [US]; PETERSON THOMAS E [US]) 30 October 2003 (2003-10-30) pages 58-61 | 12, 14-22, 24-26 |
| X | YE JING ET AL: "A protective role for heme oxygenase expression in pancreatic islets exposed to interleukin-1beta" ENDOCRINOLOGY, vol. 139, no. 10, October 1998 (1998-10), pages 4155-4163, XP002461261 ISSN: 0013-7227 page 4162 | 12, 14-22, 24-26 |
| | -/- | |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

7 December 2007

Date of mailing of the International search report

02/05/2008

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
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PCT/US2007/016023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|----------------------------------|
| X | PILEGGI ANTONELLO ET AL: "Heme oxygenase-1 induction in islet cells results in protection from apoptosis and improved in vivo function after transplantation" DIABETES, vol. 50, no. 9, September 2001 (2001-09), pages 1983-1991, XP002461262 ISSN: 0012-1797 page 1983 - page 1985 page 1989 | 12, 14-22, 24-26 |
| X | DI PASCOLI MARCO ET AL: "Chronic CO levels has a beneficial effect on vascular relaxation in diabetes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 340, no. 3, February 2006 (2006-02), pages 935-943, XP005234922 ISSN: 0006-291X the whole document | 1-4,24 |
| X | VILLA M P ET AL: "Diffusing capacity for carbon monoxide in children with type 1 diabetes" DIABETOLOGIA, vol. 47, no. 11, November 2004 (2004-11), pages 1931-1935, XP002461263 ISSN: 0012-186X the whole document | 1,2,8 |
| X | ABRAHAM NADER G ET AL: "Overexpression of human heme oxygenase-1 attenuates endothelial cell sloughing in experimental diabetes" AMERICAN JOURNAL OF PHYSIOLOGY - HEART AND CIRCULATORY PHYSIOLOGY, vol. 287, no. 6, December 2004 (2004-12), pages H2468-H2477, XP002461264 ISSN: 0363-6135 the whole document | 1,3,10, 24 |
| X | TOBIASCH EDDA ET AL: "Heme oxygenase-1 protects pancreatic beta cells from apoptosis caused by various stimuli" JOURNAL OF INVESTIGATIVE MEDICINE, vol. 49, no. 6, November 2001 (2001-11), pages 566-571, XP009093164 ISSN: 1081-5589 the whole document | 14, 16-18, 21,22, 24,26 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

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| International application No PCT/US2007/016023 |
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>WANG HONGJUN ET AL: "Bilirubin can induce tolerance to islet allografts" ENDOCRINOLOGY, vol. 147, no. 2, February 2006 (2006-02), pages 762-768, XP002461265 ISSN: 0013-7227 the whole document</p> <p>-----</p> | 12,14, 20-22, 25,26 |
| X | <p>SONG F ET AL: "Induction of heme oxygenase-1 by a natural sweetener, Momordica grosvenori Swingle, attenuates the imbalance of cellular immune functions in alloxan-induced diabetes mellitus" FEBS JOURNAL, vol. 272, no. Suppl. 1, July 2005 (2005-07), pages 463-464, XP009093207 & 30TH CONGRESS OF THE FEDERATION-OF-EUROPEAN-BIOCHEMICAL-SOCIETIES (FEBS)/9TH IUBMB CONFERENCE; BUDAPEST, HUNGARY; JULY 02 -07, 2005 ISSN: 1742-464X(print) 1742-4658(ele) the whole document</p> <p>-----</p> | 1-13, 24-26 |
| P,X | <p>HU CHIEN-MING ET AL: "Systemic expression of heme oxygenase-1 ameliorates type 1 diabetes in NOD mice" DIABETES, vol. 56, no. 5, May 2007 (2007-05), pages 1240-1247, XP002461267 ISSN: 0012-1797 the whole document</p> <p>-----</p> | 1-13, 24-26 |
| P,X | <p>LI MING ET AL: "Long-lasting expression of HO-1 delays progression of type I diabetes in NOD mice" CELL CYCLE, vol. 6, no. 5, March 2007 (2007-03), pages 567-571, XP009093214 ISSN: 1538-4101 the whole document</p> <p>-----</p> | 1-13, 24-26 |
| X | <p>GUNTHER LUKAS ET AL: "Carbon monoxide protects pancreatic beta-cells from apoptosis and improves islet function/survival after transplantation" DIABETES, vol. 51, no. 4, April 2002 (2002-04), pages 994-999, XP002461310 ISSN: 0012-1797 the whole document</p> <p>-----</p> | 1-22, 24-26 |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | WANG HONGJUN ET AL: "Donor treatment with carbon monoxide can yield islet allograft survival and tolerance" DIABETES, vol. 54, no. 5, May 2005 (2005-05), pages 1400-1406, XP002461311 ISSN: 0012-1797 the whole document ----- | 1-22, 24-26 |
| X | WANG HONGJUN ET AL: "Heme Oxygenase-1 Expression in or Carbon Monoxide Administration only to Donor Animals Can Induce Long-term Allogeneic Islet Graft Survival in Mice" FASEB JOURNAL, vol. 18, no. 4-5, 2004, pages Abst. 782.11 URL- http://www , XP009093149 & FASEB MEETING ON EXPERIMENTAL BIOLOGY: TRANSLATING THE GENOME; WASHINGTON, DISTRICT OF COLUMBIA, USA; APRIL 17-21, 2004 ISSN: 0892-6638 the whole document ----- | 1-22, 24-26 |

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2007/016023**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-22(full), 24-26(full)

Use of an agent selected from agents which induce heme oxygenase 1 (HO-1), increase the expression of HO-1, induce apo ferritin, increase the expression of apo ferritin or an agent selected from the group comprising carbon monoxide, HO-1, hemin, bilirubin, biliverdin, ferritin, iron, desferoxamine, salicylaldehyde isonicotinoyl hydrazone, iron dextran, apo ferritin for treating diabetes in patients and pharmaceutical compositions comprising these agents.

2. claim: 23(full)

The use of an agent that induces peroxisome-proliferator-activated receptor gamma (PPARK) in a patient, increases the level of expression of PPARK in a patient, or acts as a PPARK agonist or toll-like receptor 4 (TLR4) antagonist in the patient, as medicament for the treatment or prevention of diabetes.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/016023

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------|------------------|
| WO 03088745 | A 30-10-2003 | AU 2003239140 A1 | 03-11-2003 |
| | | CA 2482750 A1 | 30-10-2003 |
| | | EP 1494660 A2 | 12-01-2005 |